REMARKS

Claims 1-42 constitute the pending claims in the present application. Claims 1, 3-23, and 35-36 are withdrawn from consideration as being drawn to a non-elected invention. Applicants will cancel these claims upon indication of allowable subject matter in the elected invention. Claims 12, 24-34 and 37-40 have been amended. Support for the claim amendments is found throughout the specification and the original claims. No new matter has been added. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Specification

The Examiner asserts that "the abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4)." Applicants have amended the specification by adding an abstract on a separate sheet.

Claim rejection under 35 U.S.C. §112, first paragraph - written description

Claims 33-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Applicants submit that it is well known in the art that analogues and fragments of large molecules such as peptides (e.g., insulin) can retain the physiological function of the parent molecule, e.g., native insulin. The actual available variations on the original molecule to form the analogues or fragments can be so numerous as to be impossible to include in the patent description. However such variations will be easily conceived by one of skill in the art using common general knowledge available in the art at the time of filing. Thus, Applicants submit that it is not necessary to list the claimed specific analogues and fragments since these can easily be prepared and identified using suitable assay techniques known by the skilled artisan. Accordingly, one of skill in the art would readily recognize that analogues or fragments of peptides, such as insulin, can also be bound to a bile salt in the manner described and would be expected to be functional provided the analogue or fragment was functional prior to conjugation to the bile salt. Additionally, precisely because such analogues and fragments can be conceived and prepared by the skilled artisan without inventive activity,

and without altering significantly the physiological activity of the molecules, Applicants submit that it would be unfair to Applicants to exclude analogues and fragments from the claim scope. Under the Guidelines for the Examination of Patent Applications Under the Written Description Requirement, 66 Fed. Reg. 1104, 1105 (Jan. 5, 2001), "[i]nformation which is well known in the art need not be described in detail in the specification." Accordingly, Applicants submit that claims 33-34 are both enabled and supported by the specification as filed.

Nevertheless, Applicants have amended claim 33 without acquiescing to the Examiner's assertion, solely to focus on aspects of greatest current commercial interest. Applicants reserve the right to pursue the claims of similar or differing scope in the future.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph, are respectfully requested.

Claim rejection under 35 U.S.C. § 112, first paragraph - enablement

Claims 33-34 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse these rejections to the extent that they are maintained in light of the amended claims.

As argued above, Applicants submit that the phrase "analogues and fragments" is to cover variations in the parent or native molecule which retain the physiological activity of that molecule. The provision of analogues or fragments can be easily achieved by one skilled in the art, using, for example, recombinant techniques. Indeed, Applicants only intend to cover the analogues and fragments which retain the physiological activity of the parent or native molecule, and such can be easily tested or assayed by a skilled artisan. In particular, with regard to insulin, assays for insulin-like activity linked to blood sugar levels are well known in the art and so analogues or fragments of insulin can be easily tested for such activity. Indeed, the present invention is not directed to hitherto unknown peptides, but rather peptides with known activities which can be tested for by a skilled artisan. Thus, working examples for the analogues or fragments are not necessary in view of these principles that are well known and easily applied by the skilled person.

Nevertheless, Applicants have amended claim 33 without acquiescing to the Examiner's assertion, solely to focus on aspects of greatest current commercial interest.

Accordingly, Applicants submit that the claimed subject matter is enabled throughout its scope. Reconsideration and withdrawal of this rejection under 35 U.S.C. 112, first paragraph, are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 24-29, 32-33, 37, and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Specifically, claims 24-29, 32-33, 37, and 39-40 are objected to on the basis that there is insufficient antecedent basis for "The pharmaceutical composition" in the independent claim 2. Applicants have amended claims 24-40 to refer to "An amide according to...."

The Examiner further objects to claim 33 for the recitation of "polysaccharide." Applicants have removed the term "polysaccharide" from claim 33, thereby rendering the rejection moot.

Finally, the Examiner objects to the recitation of "analogues and fragments" in claim 33. As described above, Applicants submit that the terms "analogues and fragments" are not indefinite and clear to one of skill in the art. Nevertheless, Applicants have amended claim 33 without acquiescing to the Examiner's assertion, solely to focus on aspects of greatest current commercial interest.

Based on the amendments and arguments presented above, Applicants submit that all claims as amended comply with the requirement of 35 U.S.C. 112, second paragraph. Therefore, reconsideration and withdrawal of rejections under 35 U.S.C. 112, second paragraph, are respectfully requested.

Claim rejections under 35 U.S.C. § 103

Claims 2, 24-34 and 37-42 are rejected as being allegedly unpatentable over Byun et al (US 6245753), Kramer et al. (J. Biol. Chem. 1992, 18598-604) and Longenecker et al. (US 4994439). Applicants respectfully traverse this rejection.

First, Kramer et al. teach conjugation of drugs to bile acids. However, as a point of fact, and contrary to the Examiner's assertion, Kramer et al. do not conjugate at the C-24 position of the bile acid molecule. Applicants wish to bring the Examiner's attention to Figure 1, and the text at page 18599, 2nd column, 1st paragraph under the heading "RESULTS" where at lines 13-21 it is stated that the drugs were attached to the bile acid molecule to conserve the negatively charged side chain of the bile acids. For example, the text describes that "drugs were attached to the bile acid molecule either via an ester bond between a carboxyl group and the 3α-hydroxyl group of the bile acid or an amide bond

between the carboxyl group and a linker-modified bile acid conserving the negatively charged side chain of natural bile acids." Figure 1 confirms that the C-24 carboxyl group of the bile acids was not used in the drug conjugation; it is the 3α-hydroxyl group at the opposite end of the bile acid molecule which was used for conjugation, as specified in the text on page 18599. Kramer specifically teaches that the negative charge of the C-24 side chain should be conserved, because "a negative charge in the side chain of the bile acid molecule ... is a prerequisite" (see the first sentence under heading "RESULTS" on page 18599). The negative charge of the carboxyl group side chain of the present invention is actually destroyed by conjugating peptide molecules to that carboxyl group at the C-24 position.

By these statements, it is clear that Kramer actually teaches away from conjugating any chosen molecule at the C-24 position of the bile acid molecule as set forth in the pending claims. Furthermore, Kramer only considers conjugation of small drug molecules to bile acids. Although one of the drugs, labeled as S4404 in Figure 1, contains amide bonds, that drug is distinct from a peptide molecule such as a large protein hormone molecule, e.g., insulin, which is many times bigger than the disclosed drugs.

Second, Byun et al. teach the conjugation of a polysaccharide to the free carboxyl group of a bile acid molecule. Byun et al. do not describe, teach or suggest conjugation of peptides or insulin to bile acids. In fact, the Examiner actually acknowledges that Byun et al. do not teach conjugation of other molecules such as insulin to bile salts. It is well known in the art that polysaccharides and peptides such as insulin differ in their structures. For example, insulin is a large protein molecule which is folded into a particular three-dimensional (3D) shape and maintains that shape through various interactions between different parts of the molecule, e.g., hydrophobic interactions, hydrogen bonding and disulfide bonds. This 3D structure contributes to the physiological activity of the insulin molecule, and its disruption can destroy its biological activity. On the other hand, polysaccharides such as heparin do not form discrete, complex 3D structures which dictate the biological activity, but rather readily assume a wide spectrum of configurations. Accordingly, polysaccharides do not easily suffer from the same problems as insulin. Thus, one of ordinary skill would not even consider applying the teachings of Byun et al. to peptide molecules, but instead would consider the teaching of Byun et al. as restricted to heparin. At most, if one of ordinary skill were to generalize the teachings of Byun et al., their scope would be extended only to polysaccharides in general. Thus, Applicants submit that one of ordinary skill in the art reading the cited references would simply have no motivation to

conjugate a large peptide molecule, such as insulin, to the C-24 position of a bile acid molecule.

Third, Applicants also wish to remind the Examiner of the teaching by Swaan et al. (Bioconjugate Chem, 1997, p520-525), previously cited by the Examiner. As Applicants previously argued, Swaan specifically teaches that peptides 4 amino acid residues long were absorbed, but those of 6 amino acid residues in length were not actively absorbed. Thus, a skilled artisan is taught away from using peptides of 6 or more amino acids in length. In fact, Swaan teaches that peptides of 6 or more amino acids in length will not be actively absorbed when conjugated to bile salts. Insulin, being a large polypeptide many times bigger than a 6 amino acid peptide is thus not expected to be actively absorbed when conjugated to a bile salt. Accordingly, this reference, too, teaches away from conjugating a large molecule such as insulin to a bile acid to improve absorption.

Further, the teaching of Longenecker et al. adds nothing to the teachings of Byun et al. and Kramer et al. Longenecker et al. only teach the use of physical mixtures of the bile acid molecules with molecules to be delivered, e.g., insulin. The molecules in Longenecker et al. are not covalently conjugated. Accordingly, Longenecker et al. give no indication that covalent conjugation is even a possibility, and certainly give no suggestion as to how conjugation should be achieved and which position in the bile acid molecule should be selected for conjugation. Additionally, Longenecker et al. make use of particular surfactants to reduce the toxicity of the mixtures described (see column 2, lines 26-32). Thus, Longenecker et al. direct the skilled person to use surfactants, rather than consider conjugation of the peptide and bile acid molecules, to assist absorption across the gut mucosa.

Furthermore, Longenecker et al. only perform absorption experiments on rat nasal tissue and do not consider the complexities of oral administration into the adverse stomach/gut environment. Thus, Longenecker et al. do not show that the mixtures described can be administered orally, and certainly do not provide any expectation of success that oral administration would retain biological activity of the protein or insulin molecules.

MPEP 2142 sets forth the three basic criteria that must be met in order to establish a prima facie case of obviousness. The three criteria are that there must be some motivation to either modify the prior art reference to arrive at Applicants' invention or to combine two prior art references in order to arrive at Applicants' invention, the prior art reference or references must teach each and every limitation of the claimed invention, and there must be a reasonable expectation of success.

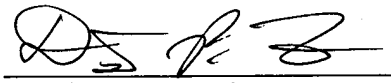
Applicants contend that the teachings of Byun et al., Kramer et al., and Longenecker et al., singularly or in combination, fail to satisfy at least two of the above three criteria, and accordingly fail to render obvious the claimed invention. Moreover, Kramer et al. and Swaan et al. actually *teach away* from the claimed invention. Accordingly, Applicants assert that the claims are not obvious in view of all cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited.

Although Applicants believe no fees are due with this submission, the Commissioner is hereby authorized to credit any overpayment or charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Respectfully Submitted,



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